Tasimelteon (Hetlioz®)

National Drug Monograph

November 2014

VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Tasimelteon is a dual melatonin receptor agonist (DMRA) selective at the MT_1 and MT_2 receptors in the hypothalamus, thereby promoting maintenance of the circadian rhythm and regulation of the sleep-wake cycle. By exhibiting greater binding affinity for the MT_2 receptor, tasimelteon regulates phase cycling and synchronizes (entrains) the body's internal biological clock back to the normal 24-hour day in order to improve sleep quality and daytime functioning. Tasimelteon and its main metabolites have no appreciable affinity for the Gamma-aminobutyric acid (GABA) complex or for receptors that bind serotonin, noradrenaline, acetylcholine, and opiates.

Indication

Tasimelteon received FDA approval on January 31st, 2014 under priority review, as an orphan drug solely for the indication of Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD). Tasimelteon is the only approved medication for N24SWD.

N24SWD

N24SWD is a circadian rhythm disorder found most commonly in blind patients with no light perception (NLP). It occurs when the individual's own biologic circadian period is not aligned to the external 24-hour environment. External cues, primarily the light/dark cycle which normally entrains the circadian rhythm to the 24-hour clock is absent in individuals with NLP. Because of that absence of input from environmental light to the eyes in patients with NLP, it causes a constant gradual shifting of the sleep-wake cycle approximately 30 minutes each day thus returning to re-alignment with the 24-hour clock only once every 48 days. Due to the lack of entrainment of the circadian rhythm, patients with NLP suffer from sleep deprivation resulting in long periods of excessive daytime sleepiness, nighttime insomnia, alterations in secretion of melatonin and cortisol, and impairment of social and occupational functioning.

Efficacy

The efficacy and safety of tasimelteon using endpoints of entrainment (aMT6s and cortisol levels) and improvement in symptoms per Non-24 Clinical Response Scale (N24CRS) were demonstrated in two phase III randomized, double-masked, placebo-controlled, multicenter trials in patients with N24SWD. The Safety and Efficacy of Tasimelteon (SET) was a 26 week trial which randomized 84 blind patients (median age 54 years) with confirmed N24SWD. Patients treated with tasimelteon 20mg (8/40) compared to placebo (1/38) achieved entrainment measured by aMT6s significantly

more in one month (20% vs 2.6%, p=0.0171). By the end of 7 months, tasimelteon entrained 59% of the patients. The primary endpoint of the Randomized-withdrawal study of the Safety and Efficacy of Tasimelteon to treat N24SWD (RESET) trial was the proportion of patients who did not maintain entrainment of an aMT6s rhythm to 24 hours after therapy was withdrawn. Twenty blind patients (median age 54 years) with N24SWD were randomized. The discontinuation of therapy following achievement of entrainment caused a loss in circadian rhythm synchronization in 80% of patients within 8 weeks.

Tasimelteon also significantly improved clinician-rated global functioning and subjective sleep parameters in this patient population, including total sleep time, nap duration, and timing of sleep.

Adverse Effects
Tasimelteon was well tolerated during clinical trials. The most common adverse reactions were headache, increased alanine aminotransferase (ALT), nightmares/unusual dreams, upper respiratory, and urinary tract infection (occurring >5% incidence and at least twice as high compared to placebo). No deaths, withdrawal, or other serious adverse events were observed during clinical trials.

Drug Interactions
- Tasimelteon is metabolized primarily by CYP1A2 and CYP3A4. The most significant drug interactions involve medications that are metabolized through these pathways such as fluvoxamine, ketoconazole, fluconazole, and rifampin.
- Smoking at least 10 cigarettes per day has shown to decrease the exposure of tasimelteon by approximately 40% and therefore the efficacy of tasimelteon may be reduced in smokers.

Monitoring
- There are no specific laboratory tests recommended.

Dosage and Administration
- Recommended Dose: 20 mg taken before bedtime, at the same time every night, without food. If the dose cannot be taken at approximately the same time on a given night, the dose should be skipped.

- Chronic therapy with tasimelteon 20 mg is required to maintain entrainment in patients with N24SWD. Because of individual differences in circadian rhythms, complete drug effect is variable. An initial course of at least 6 months is recommended to determine efficacy in individuals.

Dose Considerations:
- Gender:
  - The mean overall exposure of tasimelteon was approximately 20-30% greater in female than in male subjects. No dose recommendation is provided.
- Geriatric:
  - The mean overall exposure of tasimelteon was approximately 2-fold greater in elderly (>65 years old) than in younger patients. No dose recommendation is provided.

- Smokers:
  - The exposure of tasimelteon in tobacco smokers was approximately 40% lower than in non-smokers, therefore efficacy may be reduced and a dose adjustment may be considered.
- Mild or moderate hepatic impairment:
  - No dose adjustment necessary.
- Renal impairment of any degree:
  - No dose adjustment necessary including patients undergoing chronic hemodialysis.
- Concomitant administration of Beta adrenergic receptor antagonists:
  - The efficacy of tasimelteon in treating N24SWD may be reduced.

Conclusions:

Tasimelteon is the only FDA approved agent for Non-24 Hour Sleep-Wake Rhythm Disorder. Studies have confirmed its efficacy and safety in blind patients with NLP. It should not be used for the treatment of any other sleep conditions. Tasimelteon has a short half-life, high MT_2 receptor binding, and is a circadian regulating agent that entrains circadian rhythms to the 24-hour clock by its discrete signaling in the suprachiasmatic nucleus. Clinical trials have shown objective clinical markers of improvement via aMT6s and cortisol levels. Subjective indicators including improved nighttime sleep, daytime naps, and timing of sleep were also observed. Tasimelteon was well tolerated, with no serious adverse events reported in trials. Due to individual difference in circadian rhythms, daily use for several weeks or months may be necessary before entrainment of circadian rhythm is achieved. Daily use is required to maintain entrainment of circadian rhythms.

Introduction[1-11]

Tasimelteon is a dual melatonin receptor agonist (DMRA) approved by orphan status as the first agent for the indication of Non-24-hour Sleep-Wake Rhythm Disorder (Non-24; ICD-9 307.45 - *Circadian rhythm sleep disorder of nonorganic origin*). By exhibiting greater binding affinity for the MT_2 receptor, tasimelteon regulates phase cycling and entrains the body's internal biological clock back to the normal 24-hour day. N24SWD is a rare chronic circadian rhythm disorder that most often occurs in totally blind individuals and is characterized by cycling through periods of excessive daytime sleepiness and nighttime insomnia.

During nighttime hours, the pineal gland endogenously synthesizes melatonin as a response to darkness. Conversely, light causes the suprachiasmatic nucleus (SCN) to inhibit the production of melatonin. Totally blind patients, often termed no light perception (NLP), suffer from sleep deprivation due to the absence of input from environmental light to the eyes that de-synchronizes the internal circadian rhythm usually resulting in a cyclic progression of sleep latency. Thus, the individual's own biologic circadian period is not aligned to the external 24-hour environment and they tend to continuously fall asleep an average of 30 minutes (range: -12 to 66 minutes) later each night, resulting in realignment approximately every 48 days. Over time, physiological changes occur such as alterations in secretion of melatonin and cortisol hormones, abnormal insulin secretion and insulin resistance in muscle, mood disorders, cardiovascular disease, obesity, nutrient malabsorption, and electrolyte imbalances.

Due to a lack of stable sleep time, this condition can be extremely debilitating and difficult maintaining a normal daily routine compatible with a sighted 24 hour society. Furthermore, patients may experience long-term health effects of sleep deprivation including excessive daytime sleepiness, depression, anxiety disorders, weight gain, diabetes, difficulty concentrating and performing everyday functions, social isolation, and increased risk of mortality.

The Diagnostic and Statistical Manual (DSM)-5 criteria for the diagnosis of N24SWD is based on a history of symptoms, daily sleep logs, and ruling out other medical or substance use disorders. Epidemiologic studies estimate that 50-70% of NLP individuals in the United States suffer from N24SWD. De l'Aune et al.[5] (1999) conducted a demographic and outcome-based survey of 3000 visually impaired Veterans enrolled in VA-sponsored Blind Rehabilitation Programs and it was determined that approximately 9% of legally blind Veterans have no light perception. Anticipating that the base percentage of NLP patients has not changed in any appreciable way, and applying the total number of Veterans currently being case managed by Visual Impairment Service Team Coordinators (n= 50,561), it is estimated that potentially 4,550 Veterans are NLP (2014 data). (M. Williams, Ph.D., Blind Rehabilitation Service National Program Office personal communication, September 29-October 21, 2014). Applying the same base percentage of 9% NLP to the total number of legally blind Veterans residing in the United States in 2014 (n=132,805) irrespective of enrollment, approximately 12,000 Veterans have no light perception and 6,000 to 8,400 of these Veterans could potentially experience Non-24 Sleep-Wake Rhythm Disorder.

In March 2015, an internal ICD Diagnostic Request for N24SWD was conducted using ICD-CM 307.45. It was determined for FY13-14, 200 unique patients were found in the system to have this diagnostic code.

The purposes of this monograph are to (1) evaluate the evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating the possible addition of tasimelteon to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

FDA Approved Indication(s)[8-9,11]

Tasimelteon is FDA approved as a melatonin receptor agonist indicated for the treatment of Non-24-Hour Sleep-Wake Rhythm Disorder (N24SWD).

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA Center for Medication Safety, VHA PBM-MAP-VPE and Guidance on "Off-label Prescribing (available on the VA PBM Intranet site only).
It was granted orphan status for treatment of sleep disturbances associated with Smith-Magenis Syndrome in 2010. Tasimelteon could potentially be utilized off-label for insomnia (primary or transient) or other circadian rhythm sleep-wake disorders (jet lag, advanced or delayed phase disorders, and work shift disorder) refractory to melatonin.

Current VA National Formulary Alternatives

No current VA formulary alternatives exist.

Pharmacology[1-3,8-12]

Tasimelteon is a dual melatonin receptor agonist (DMRA) selective at MT_1 and MT_2 receptors in the suprachiasmatic nucleus (SCN) of the hypothalamus. Endogenously, melatonin acts on both MT_1 and MT_2 receptors and is thought to be involved in the maintenance of the circadian rhythm, which regulates the sleep-wake cycle as well as contributes to several neurodegenerative diseases, mood disorders, pain, and insomnia. Although the specific functions of each receptor have yet to be realized, it is hypothesized that the MT_1 receptor is involved with sleep initiation through an inhibitory effect on neuronal firing and suppression of wake-related neuronal pathways. Conversely, it is speculated that when melatonin acts upon the MT_2 receptor, it has a time-dependent effect on the SCN circadian rhythm, regulating the circadian phase-shifting. Tasimelteon exhibits 2.1 to 4.4 times greater binding affinity for the MT_2 receptor compared to the MT_1 receptor. Therefore, by exhibiting greater binding affinity for the MT_2 receptor, tasimelteon acts as a sleep switch to entrain the circadian rhythm back to 24-hour day thereby promoting synchronization of sleep and wake schedules and realignment of circadian rhythm hormones and physiological functions.

- The most abundant metabolites of tasimelteon are M_3, M_9, and M_{11}- M_{14}. These metabolites are active but have a ≤13-fold lower activity compared to the parent molecule for both the MT_1 and MT_2 receptors. In comparison, melatonin and ramelteon have a stronger binding affinity for MT_1 than MT_2 receptors.
- Tasimelteon and its main metabolites have no appreciable affinity for the GABA complex or for receptors that bind serotonin, noradrenaline, acetylcholine, and opiates.

Pharmacokinetics[2-3,8-9,11]

Table 1: Pharmacokinetic (PK) Parameters in Adults

Parameters	Tasimelteon
Basic PK Model	Linear over doses ranging from 3 to 300 mg
T_{max} (h)	Fasting: 0.5-3
Elimination	80% urine (<1% excreted as parent compound)
	4% feces
Mean Elimination half-life (h)	1.3 ± 0.4 in healthy adults
Distribution	90% protein bound
Volume of Distribution (L)	56 to 126
Metabolism	Extensively and rapidly metabolized by CYP1A2, CYP3A4, phenolic glucoronidation (major) and CYP1A1, CYP2D6, CYP2C19, and CYP2C9 (minor).
Bioavailability	Not established
Effect of Food	The median T_{max} was delayed by ~1.75 hours and the C_{max} was 44% lower with a high-fat meal compared to the fasted state.

Dosage and Administration[2-3,8-9,11]

General Recommendations: The recommended dosage of tasimelteon is 20 mg per day taken before bedtime, at the same time every night without food in adults ≥ 18 years of age. If the dose cannot be taken at approximately the same time on a given night, the dose should be skipped. Because of individual differences in circadian rhythms, complete drug effect may not occur for weeks or months. An initial course of at least 6 months is recommended to determine efficacy in individuals.[+] Discontinuation of therapy following achievement of entrainment causes a loss in circadian rhythm synchronization in 80% of patients within 8 weeks.

[+]Cycle lengths generally ranged from 27-184 days. Based on 1 standard deviation from the mean, the majority of patients studied had a cycle length of 40-80 days.[6]

Table 2: Special Populations and Considerations for Tasimelteon [2-3,8-9,11]

Geriatric Use (>65 years old)	Exposure is increased by ~2-fold compared with younger patients increasing the potential risk of adverse reactions. No dose recommendation is provided.
Hepatic Impairment	Dose adjustment is not required in patients with mild (Child-Pugh Scores ≥ 5 and ≤ 6); or moderate hepatic impairment (Child-Pugh Scores ≥ 7 and ≤ 9), The use is not recommended in patients with severe hepatic impairment (Child-Pugh Class C).
Renal Impairment	Clearance is 30% lower in severe renal impairment (eGFR < 30 ml/min/1.73 m^2). Dose adjustment is not required in patients with renal impairment of any degree, including in severe renal impairment or hemodialysis.
Tobacco Smokers	Exposure is decreased by ~40% compared to non-smokers due to induction of CYP1A2. Efficacy may be reduced in smokers, therefore a dose adjustment may be considered.
Gender	The mean overall exposure of tasimelteon was approximately 20-30% greater in female than in male subjects. No dose recommendation is provided.
Pregnancy Category	C; Administration is not recommended.
Nursing Mothers	It is unknown whether tasimelteon is excreted in human milk.
Pediatrics	The safety and efficacy has not been evaluated.

Efficacy[8-9,11-22]

The efficacy of tasimelteon was measured using endpoints of entrainment (urinary 6-sulfatoxy-melatonin and cortisol levels) and improvement in symptoms per Non-24 Clinical Response Scale (N24CRS) in two phase III randomized, double-masked, placebo-controlled, multicenter trials; the Safety and Efficacy of Tasimelteon (SET) and the Randomized-withdrawal study of the Safety and Efficacy of Tasimelteon to treat Non-24 (RESET).

Efficacy Measures:

- Urinary 6-sulfatoxy-melatonin (aMT6; metabolite of melatonin)
  - Melatonin peaks at night and is not masked by other factors except light which suppresses melatonin. It is considered the gold standard for the measurement of entrainment of circadian rhythm in humans.
- Cortisol
  - Cortisol peaks in the morning. It is key regulatory hormone in the body which exhibits a strong circadian rhythm and is another objective measure of entrainment.
- Non-24 Clinical Response Scale (N24CRS)
  - 4-item scale that assesses the following sleep-wake parameters and patient functioning:
    1. LQ-nTST- Lower Quartile of Nights of Total Sleep Time
       - Improvement in the nTST in the worst 25% of nights
    2. UQ-dTSD-Upper Quartile of Days of Total Sleep Duration
       - Decrease in the dTSD in the worst 25% of days
    3. MoST-Weighted midpoint of sleep timing
       - Measures timing and consolidation of patient's sleep; an increase in MoST represents an improvement
    4. CGI-C-Clinical Global Impression of Change
       - Validated clinician-rated seven point scale used to assess the overall impact of Non-24 symptoms on patient functioning; lower scores indicate greater improvement
  - The worst 25% of nights and days are evaluated using LQ-nTST, UQ-DTSD due to the cyclical nature of the symptoms of Non-24.
  - Each item is scored as a 1 or a 0 depending on whether the pre-specified threshold was met or not. Refer to Table 3 for threshold definitions. To be

considered a responder for the N24CRS, patents need to experience improvement on at least three of the four measures.

Table 3: Pre-specified Thresholds*

Assessment	Threshold of Response
LQ-nTST	≥ 45 minutes increase in average nighttime sleep duration
UQ-dTSD	≥ 45 minutes decrease in average daytime sleep duration
MoST	≥ 30 minutes increase and a standard deviation ≤ 2 hours during double-masked phase
CGI-C	≤ 2.0 score for average of days 112 and 183 versus baseline

*LQ-nTST= Total nighttime sleep in the worst 25% of nights; UQ-dTSD= Total daytime sleep duration in the worst 25% of days; MoST= Weighted midpoint of sleep timing; CGI-C= clinical global impression of change

Safety and Efficacy of Tasimelteon (SET) Trial[8-11,15,18]

- **Design:** Phase III, multicenter, randomized, double-masked, placebo-controlled trial conducted between August 2010 and October 2012. Patients ineligible for randomization or unable to complete the trial could elect to participate in the open-label extension phase.
- **Objective:** To investigate the safety and efficacy of tasimelteon in patients with Non-24
- **Population**: 84 totally blind individuals with confirmed N24SWD (as defined by aMT6 rhythms) aged 18-75 years; (mean age 51±13 years; 58% male; 83% Caucasian, 12% African American, mean BMI 27.95 kg/m^2 ; average circadian rhythm= 24.7 hours). No notable differences were seen between treatment and placebo groups.
- **Intervention:** Patients were randomized to receive either tasimelteon 20 mg (n=42) or placebo (n=42) 1 hour before bedtime for 26 weeks. Treatment was initiated after a variable-length in-phase transition (~ 3 months) and not until the patient's circadian phase was aligned with their target bedtime.
- **Primary efficacy endpoint**
  - Proportion of patients who experienced entrainment to a 24-hour rhythm, as defined by urinary aMT6s levels.
- **Step-down Primary Outcome**
  - Clinical response, as defined as the coincident demonstration of entrainment (τ <24.1) and a score of $\geq$ 3 on the N24CRS.
- **Secondary Efficacy Endpoints**
  - Proportion of patients who experienced entrainment, as defined by urinary cortisol levels
  - Global function, as assessed using the Clinical Global Impression of Change
  - Clinical sleep and wake parameters assessed twice a day via an interactive voice recording system
- **Results:** *Refer to Appendix A, Table 1 for details.*
  - **Population:** A total of 391 patients were screened for eligibility, of which 84 were randomized to receive either tasimelteon 20 mg or placebo. Twenty-two patients did not complete the study: adverse events (n=6), protocol deviation (n=1), withdrawal of consent (n=5), and unsatisfactory response (n=1); travel issues (n=1); study closed by sponsor but patients had adequate data for primary and secondary endpoints in the double-masked phase (n=8; 4-tasimelteon; 4 placebo).
  - **Primary endpoint:** Significantly more patients treated with tasimelteon 20mg (8/40) compared to placebo (1/38) achieved entrainment measured by aMT6s in one month (20% vs 2.6%, p=0.0171).

- **Step-down primary endpoint:** Entrainment was assessed at month 1 as well as month 7, during the tasimelteon open label phase. A significant clinical response was achieved in patients taking tasimelteon compared to placebo, respectively, 23.7% (9/38) versus 0% (0/34), p=0.0028.
- **Secondary endpoints:** Significantly more patients treated with tasimelteon compared to placebo achieved entrainment based on cortisol levels (7/20; 17.5% versus 1/38; 2.6%, p=0.0313), respectively. The patients in the tasimelteon group improved significantly in total sleep time, nap duration, timing of sleep, and global functioning compared to placebo.
- **Post-hoc analyses** requested by FDA were conducted for LQ-nTST and UQ-dTSD using all randomized patients. Results demonstrated that LQ-nTST (nighttime sleep on 25% most symptomatic nights) improved by 50 minutes compared to 22 minutes for placebo (p=0.051) and UQ-dTSD (daytime sleep on 25 % most symptomatic days) decreased by 49 minutes compared to 22 minutes for placebo (p=0.012). A clinical response was demonstrated by 12/42 (29%) of the tasimelteon group compared to 5/42 (12%) in the placebo group as measured by LQ-nTST + UQdTSD ≥45 minutes, p=0.064.

Randomized withdrawal study of the Efficacy and Safety of Tasimelteon: (RESET)[8-9,11,16]

- **Design:** Phase III, multicenter, randomized withdrawal, double-masked, placebo-controlled, parallel group designed to determine the long-term maintenance effect and safety of tasimelteon 20 mg in patients with Non-24. The study consisted of two phases: 1) open label pre-randomization phase (~12 weeks), and 2) placebo-controlled randomized withdrawal phase (~8 weeks).
- **Objective:** Demonstrate effectiveness and safety of tasimelteon 20mg in maintaining entrainment when treatment was withdrawn.
- **Population:** Patients meeting inclusion criteria and who had previously participated in, or were screened for SET trial, were eligible to participate. Twenty entrained totally blind individuals (as defined by aMT6 rhythms) were randomized (aged 27-68 years; (mean age 51.7years; 60% male; 90% Caucasian, 5% African American, mean BMI 28.64 kg/m^2; mean circadian rhythm= 24.0 hours). No demographic or patient characteristics differences between the two groups exist.
- **Intervention:** Patients continued tasimelteon 20 mg nightly for 6 weeks to ensure entrainment was achieved. Patients who demonstrated entrainment (based on aMT6 levels) were randomized to receive either tasimelteon 20 mg or placebo nightly for 8 weeks.
- **Primary endpoint:** Proportion of N24SWD patients who did not maintain entrainment of circadian rhythms as measured by urinary aMT6s after therapy was withdrawn. (Non-entrainment was defined as having a post-baseline $\tau \geq 24.1$ or the lower bound of the 95% CI>24.0 hours)
- **Secondary endpoints:** Proportion of N24SWD patients with non- entrainment measured by urinary cortisol levels; and subjective nighttime sleep parameters (nTST, LQ-nTST); daytime sleep parameters (dTSD, UQ-dTSD; MoST)

Results: *Refer to Appendix A, Table 2 for details.*

- **Population results:** 20 patients were included in the randomized withdrawal phase; 10 were randomized to each treatment group and all 20 completed the study.

- **Primary efficacy results:** Rate of non-maintenance of entrainment was significantly lower in tasimelteon treated patients compared to placebo based on aMT6 levels, respectively, (10% of vs. 80%; p=0.0026).
- **Secondary efficacy results:** Non-maintenance of entrainment occurred significantly less in tasimelteon treated patients compared to placebo based on cortisol levels respectively, (20% vs. 80%; p=0.0118). Tasimelteon maintained improvement in nighttime and daytime sleep parameters, and was significantly associated with the delay of relapse in total sleep time.
  - **LQ-nTST:** Nighttime total sleep duration in the worse quartile nights was significantly longer in patients who received tasimelteon compared to placebo (by 67 minutes, p=0.0233).
  - **dTSD:** Patients who received placebo experienced an increase in daytime sleep duration by 17.85 minutes, whereas those who received tasimelteon experienced a further reduction in daytime sleep duration by 3.12 minutes compared to the run-in phase (treatment difference = -20.97 minutes, p=0.0547).
  - **UQ-dTSD:** Daytime total sleep duration in the worst quartile of days was 49.95 minutes longer in patients receiving placebo, and 9.31 minutes shorter in patients receiving tasimelteon (treatment difference = -59.25 minutes, p=0.0266).
  - **MoST:** Treatment with placebo resulted in a decrease in midpoint of sleep timing by 16.05 minutes, while treatment with tasimelteon resulted in a further increase in midpoint of sleep timing by 19.99 minutes (treatment difference= 36.04 minutes, p=0.0108).
  - **Non-entrained and ≥ 30 minute decrement in nTST**: 10% of the patients taking tasimelteon vs. 50% in the placebo (% difference = -40.0, p=0.0623.
  - **Time to relapse:** Relapse is defined as experiencing a ≥45 minute decrement in weekly average subjective nTST compared to the run-in phase. A higher percentage of patients in the placebo group had a relapse event and at an earlier time point. All of the placebo patients who relapsed did so by the time they were halfway through their circadian cycle (e.g. when their body clock was most out of synchrony with the 24-hour day).
- **Conclusion**: Significantly more patients who continued treatment with tasimelteon maintained entrainment, as measured by aMT6 and cortisol levels. Patients who discontinued tasimelteon treatment experienced a significant decrease in nighttime sleep duration in the worst quartile of nights, along with a significant increase in excessive daytime sleep duration in the worst quartile of days. These patients also experienced a significantly negative impact on the timing of sleep relative to desired bedtimes. This demonstrates that in order to maintain entrainment and clinical improvements in sleep-wake parameters, ongoing treatment with tasimelteon is required.

Table 4: Summary of Efficacy Findings[11-12, 17]

Study	Endpoint	Tasimelteon	Placebo	p value
SET[2,10, 27]	**Primary**			
	Entrainment (month 1-aMT6s)	20.0%	2.6%	0.0171
	Step-Down Primary			
	Entrainment (month 1 or month 7) + N24CRS $\geq$ 3	23.7%	0%	0.0028
	Secondary			
	Entrainment (month 1-cortisol)	17.5%	2.6%	0.0313
	LQ -nTST (LS mean minutes)[a]	56.80	17.08	0.0055
	UQ- dTSD (LS mean minutes)[a]	-46.48	-17.87	0.0050

	MoST (LS mean minutes)[a]	35.0	14.48	0.0123
	CGI-C (LS mean)	2.6	3.4	0.0093
RESET[10,18, 27] (Withdrawal Study)	**Primary**			
	Loss of Entrainment (week 8-aMT6)	10%	80%	0.0026
	Secondary			
	Loss of Entrainment (week 8-cortisol)	20%	80%	0.0118
	Worsening nTST[b]	10%	50%	0.0623
	LQ-nTST (LS mean minutes)[a]	-6.74	-73.74	0.0233
	dTSD (LS mean minutes)[a]	-3.12	17.85	0.0547
	UQ-dTSD (LS mean minutes)[a]	-9.31	49.95	0.0266
	MoST (LS mean minutes)[a]	19.99	-16.05	0.0108
	Time to relapse[c] (median weeks)	NE	4	0.1481

[a]LS mean=least-squares mean; [b]Worsening of nTST is defined as non-entrainment and a ≥ 30 minute decrement in nTST; [c]Relapse is defined as experiencing a ≥ 45 minute decrement in weekly average subjective nTST compared to the run-in phase.

Abbreviations: aMT6s= 6-sulfatoxy-melatonin; N24CRS=Non-24 Clinical Response Scale; LQ-nTST= lower quartile of nighttime total sleep time; UQ-dTSD= upper quartile of daytime total sleep duration; MoST= midpoint of sleep timing dTSD; CGI-C= Clinical Global Impression of Change; NE=Not estimable; SET=Safety and Efficacy of Tasimelteon;.RESET=Randomized Withdrawal study of the Safety and Efficacy of Tasimelteon.

For further details on the efficacy results, refer to *Appendix A: Clinical Trials*

Adverse Events (Safety Data)[2-3,11,15-19,22]

A total of 1346 patients were treated with tasimelteon during clinical trials, of which 139 patients received treatment for >26 weeks and 93 patients received treatment for > 1 year. Overall, tasimelteon has been well-tolerated and safe in clinical trials. The majority of adverse events were mild or moderate.

Table 5: Adverse Events* from SET and RESET Trials[8,14]

Adverse Events	Tasimelteon 20mg N=52	Placebo N=52
Headache	8 (15.4%)	3 (5.8%)
Alanine aminotransferase increased	5 (9.6%)	2 (3.8%)
Vivid or Unusual Dreams	4(7.7%)	0
Somnolence	3 (5.8%)	1 (1.9%)
Upper Respiratory tract infection	3 (5.8%)	0
Urinary tract infection	3(5.8%)	1 (1.9%)
Conduction disorder	3(5.8%)	0
Sleep disorder	3 (5.8%)	0

*Events occurring in at least 5% tasimelteon group and in at last 2X frequency of placebo

Table 6: Overview of Safety Outcome Data

	SET Trial[11,18]		RESET Trial[11,19]	
	Tasimelteon (n=42)	Placebo (n=42)	Tasimelteo (n=10)	Placebo (n=10)
Any AE, n (%)	34 (81.0%)	24 (57.1%)	6 (60%)	4 (40%)
Any treatment-related AE*, n (%)	19 (45.2%)	15 (35.7%)	4 (40%)	2 (20%)
Any SAE, n (%)	2 (4.8%)	0 (0%)	0 (0%)	0 (0%)
Any treatment-related SAE*, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Discontinuation due to any AE, n (%)	3 (7.1%)	2 (4.8%)	0 (0%)	0 (0%)
Discontinuation due to treatment-related AEs,* n (%)	3 (7.1%)	1 (2.4%)	0 (0%)	0 (0%)
Death, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

*Treatment-related indicates all events in which the relationship with study drug was assessed by the investigator as certain, probable, possible, or unassessable. AE= Adverse event; SAE= Significant adverse event.

Deaths and Other Serious Adverse Events

No deaths or other serious adverse events occurred in either the tasimelteon treated or placebo treated groups during clinical trials.

Common Adverse Events
The most common adverse event reported in >10% of patients in clinical trials was headache. Other common adverse events include increased aminotransferase, abnormal dreams, upper respiratory tract infection, and urinary tract infection.

Tolerability
Tasimelteon was generally well tolerated in adults with Non-24. In phase III clinical trials, discontinuation due to adverse events was 5.7% in those treated with tasimelteon versus 3.8% in those treated with placebo. No evidence of tolerance, withdrawal effects, rebound, or next-day residual effects has been found with tasimelteon in clinical trials.

For further details on the safety results of the clinical trials, refer to *Appendix A: Clinical Trials.*

The safety and efficacy of tasimelteon has also been evaluated in several phase II and phase III trials for other off-label indications, including transient insomnia, primary insomnia, and major depressive disorder.[10-11,23]

Transient Insomnia (Abstracts)[24]
Two studies have investigated the efficacy and safety of tasimelteon for treatment of transient insomnia associated with sleep-time shift, such as with jet lag or work shift circadian rhythm disorder types.

In a phase II randomized, double-blind, placebo-controlled 8-day inpatient study, 39 healthy participants aged 18-50 years were randomized to receive tasimelteon 10mg, 20mg, 50mg, 100mg or placebo. Patients were in a light controlled time isolation sleep facility. Following a 3-day lead-in period with placebo, the sleep episode was then advanced by 5 hours for the next 3 consecutive nights. The primary efficacy objective was sleep efficiency on day 1. Secondary outcome measurements were wake after sleep onset (WASO), and latency to sleep onset. The primary outcome measure for circadian timing was dim-light melatonin onset ($DLMO_{25\%}$). Tasimelteon significantly increased the polysomnographic sleep efficiency on day 1, (50 mg and 100 mg, $p<0.05$), reduced latency to sleep onset (10 mg, 20 mg, 50 mg; $p<0.05$; 100 mg; $p<0.01$), compared to placebo. No statistical difference was seen in the WASO outcome with tasimelteon compared to placebo. On days 2 and 3, no statistical difference was seen in sleep efficiency measurement with any dose of tasimelteon compared to placebo. While all doses of tasimelteon shifted the circadian melatonin rhythm on the first night of treatment, only tasimelteon 100mg significantly shifted it earlier compared to placebo; $p=0.001$. The frequency and severity of adverse effects were similar across all treatment groups. No difference in next-day residual effects was observed as measured by psychomotor vigilance test between the treatment and placebo groups (data not shown).

In a phase III randomized, double-blind, placebo-controlled study, 411 healthy participants with transient insomnia induced in a sleep clinic (5 hour phase shift) were randomized to tasimelteon 20 mg, 50 mg, 100 mg or placebo 30 minutes prior to sleeping. Polysomnographic latency to persistent sleep was the primary efficacy outcome. All doses of tasimelteon significantly decreased the primary outcome compared to placebo, $p<0.01$). Although not prespecifed as an outcome, WASO was decreased with tasimelteon 20 mg; ($p<0.05$) and 50 mg; ($p<0.01$) compared to placebo group but not the 100 mg dose. No difference in next-day residual effects was observed

as measured by digit symbol substitution test between the treatment and placebo groups (data not shown).

Primary Insomnia (Abstract)[19]
A phase III, multicenter, randomized, double-masked, placebo-controlled parallel group clinical trial investigated the safety and efficacy of tasimelteon in the treatment of 322 adult patients with primary insomnia with difficulty falling asleep using objective and subjective and measurements. Patients were randomized to receive tasimelteon 20mg, 50mg, or placebo 30 minutes prior to sleep for 5 weeks. The primary endpoint, mean improvement in latency to persistent sleep on Nights 1 and 8 significantly improved from baseline with both tasimelteon 20mg and 50mg compared to placebo; $p<0.001$. No difference was found in rebound or next morning residual effects between tasimelteon and placebo (data not shown).

Major Depressive Disorder[23]
A randomized, double-blind, placebo-controlled trial investigated the efficacy of tasimelteon in major depressive disorder. A total of 607 patients diagnosed with major depressive disorder were randomized to either tasimelteon 20mg once daily or placebo. At 8 weeks, tasimelteon did not meet the primary endpoint of change in Hamilton Depression Scale.

Contraindications[8-9,11]

None

Warnings and Precautions[8-9,11]

Somnolence: After taking tasimelteon, patients should limit their activity to preparing for going to bed. Tasimelteon can potentially impair the performance of activities requiring complete mental alertness.

Sentinel Events

None

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment	Risk Potential
Tasimelteon	None	None	None	Ramilteon Tamsulosin Temazepam	Low
Hetlioz®	None	None	None	Halcion	Low

Drug Interactions[2-3,8-9,11]

Drug-Drug Interactions
Tasimelteon is metabolized primarily at CYP1A2 and CYP3A4. The most significant drug interactions involve medications which are metabolized through these pathways.

Tasimelteon is also minimally metabolized through CYP1A1, CYP2D6, CYP2C19, and CYP2C9 resulting in possible additional drug interactions.

Ketoconazole (CYP3A4 inhibitor)
Tasimelteon exposure increased by approximately 50% when co-administered with ketoconazole 400 mg (after 5 days of ketoconazole 400 mg per day).

Rifampin (strong CYP3A4 and moderate CYP2C19 inducer)
The exposure of tasimelteon decreased by approximately 90% when co-administered with rifampin 600 mg (after 11 days of rifampin 600 mg per day). Avoid use in combination with rifampin or other CYP3A4 inducers because of a potentially large decrease in tasimelteon exposure with reduced efficacy.

Fluvoxamine (strong CYP1A2 inhibitor)
The $AUC_{0\text{-}inf}$ and C_{max} of tasimelteon increased by 7-fold and 2-fold, respectively, when co-administered with fluvoxamine 50 mg (after 6 days of fluvoxamine 50 mg per day). The combination with fluvoxamine or other strong CYP1A2 inhibitors should be avoided because of a potentially large increase in tasimelteon exposure and greater risk of adverse reactions.

Rosiglitazone (CYP2C8 substrate)
The administration of tasimelteon 20 mg once a day for 16 days did not produce any clinically significant changes in the T_{max}, C_{max}, or AUC of rosiglitazone after oral administration of 4 mg. This indicates that there is no induction of CYP2C8 by tasimelteon at this dose.

Alcohol
When ethanol was co-administered with 20mg of tasimelteon to healthy subjects, tasimelteon had no additive effect on psychomotor performance or memory task.

Smokers
When 20mg of tasimelteon was administered to 24 subjects who smoked at least 10 cigarettes per day, tasimelteon exposure decreased by approximately 40% as compared to the exposure in subjects who did not smoke.

Drug-Lab Interactions
Tasimelteon is not known to interfere with commonly used clinical laboratory tests.

Drug-Food Interactions
When administered with a high-fat meal, the C_{max} of tasimelteon was 44% lower than when given in a fasted state, and the median T_{max} was delayed by approximately 1.75 hours. Therefore, tasimelteon should be taken without food.

Pharmacoeconomic Analysis[9,11]

An economic model for tasimelteon in Non-24 is under development per manufacture's dossier. Results are expected at the end of 2015.

Use of Melatonin in N24SWD[25-36]

It is generally accepted that exogenous melatonin synchronizes and shifts the phases of various human circadian rhythms. The optimal dose of melatonin to produce the desired phase advance shifts or phase delay shifts has been conducted using doses as low as 0.3 mg in N24SWD patients to 3 mg in normal healthy adults. It is usually accepted that low oral dose of 0.5mg melatonin daily is effective at entraining the free-running circadian systems in most of the studies with blind patients. It is hypothesized that using high dose melatonin will cause a supraphysiologic concentration which will be difficult to recognize at the receptor level and may also produce numerous biological effects including daytime sleepiness, impaired mental and physical performance, hypothermia, and hyperprolactinemia. Findings from a variety of studies using melatonin for N24SWD indicate that treatment is optimal when melatonin is administered at the correct circadian phase. When melatonin is administered in the phase advance portion of the phase response curve, most free-running subjects will entrain, whereas when melatonin is initially given in the phase delay portion, the majority of these patients will not entrain. Taking melatonin at bedtime, as a sleep aid, will have a relatively minor effect on circadian phase so administering melatonin about 5 hours before the desired bedtime is recommended to achieve entrainment for the majority of N24SWD patients.

A meta-analysis with the critical outcome of entrainment using melatonin was included in the recent American Academy of Sleep Medicine Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders. Three placebo-controlled, crossover studies using timed oral melatonin for patients with N24SWD (n=36) were included in the meta-analysis. The dose of melatonin studied included 0.5mg, 5 mg, and 10mg and the duration of melatonin treatment ranged from 26-81 days. The odds ratio for entrainment was 21.18 (95% CI 3.22-139.17) in favor of melatonin. Although the quality of evidence was low and the strength of the recommendation was weak for, the recommendation that clinicians use strategically timed melatonin for the treatment of N24SWD in blind adults (versus no treatment) was made based on the assessment of evidence, benefits versus harms analyses, and patient values and preferences.

Conclusion

Tasimelteon is a dual melatonin receptor agonist (DMRA) and is currently the only FDA approved medication for the treatment of N24SWD. Clinical trials have shown a significant increase in entrainment to a 24-hour cycle in totally blind patients with Non-24 hour sleep-wake disorder with tasimelteon 20 mg compared to placebo. Tasimelteon 20 mg is effective at clinically improving many sleep/wake parameters (decrease daytime naps/increase total sleep time) and global functioning in blind patients with Non-24.

Tasimelteon is generally well tolerated, with the most common adverse event being headache (incidence of 17% in tasimelteon and 7% in placebo). Other side effects include increased aminotransferase, abnormal dreams, upper respiratory tract infection, and urinary tract infection, all of which had an incidence of 10% or less.

Discontinuation of therapy following achievement of entrainment caused a loss in circadian rhythm synchronization in 80% of patients within 8 weeks. Chronic therapy with tasimelteon 20 mg is required to maintain entrainment in patients with N24SWD.

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Appendix A: Clinical Trials

Table 1: Safety and Efficacy of Tasimelteon (SET) [8-9, 11,16,18]

Study Goal	Evaluate the efficacy and safety of a 26-week treatment of tasimelteon 20mg vs. placebo in subjects with Non-24-Hour Sleep-Wake Disorder.
	Study Design • A multicenter, randomized, double-masked, placebo-controlled, parallel study conducted at 33 sites in the United States and Germany between August 2010 and October 2012. The study comprised on average 3 months pre-randomization phase for screening and circadian rhythm phase transition, a 6-month randomized, double-masked treatment phase and an optional 6-month open-label extension. • Entrainment was determined from weighted regression analysis of the peak timing of urinary aMT6s collected in 4-8 hour intervals for 48 hours per week for 4 weeks starting 14 days after treatment to assess entrainment status early In order to minimize missing data. • Non-24 patients with circadian period (τ) of greater than 24.0 hours but outside the inclusion criteria limits were given the option to participate in the Open-Label Extension Phase (OLE) directly from screening. • Patients completing the double-masked treatment could also elect to participate in the OLE or the RESET study. **Study Endpoints:** • Primary efficacy endpoint: Proportion of entrainment of the urinary 6-sulfatoxymelatonin (aMT6s) rhythm to 24 hours at 1 month • Step-down primary endpoint: Clinical response as defined as the coincident demonstration of entrainment rhythm at month 1 or 7 and a score of ≥3 on the N24CRS. • Secondary efficacy endpoint: Proportion of entrainment as assessed by urinary cortisol rhythm, improvement of subjective nighttime total sleep time (nTST) assessed by the change from screening in the average of LQ-nTST; reduction of subjective daytime total sleep time (dTSD) assessed by a change from screening in the average of UQ-dTSD; change from the screening in MoST; CGI-C. **Data Analysis** • Success of the trial was based on the rejection of the null hypothesis (alpha level of 0.05) associated with the proportion of entrainment as measured by aMT6s. • Data were summarized by treatment group, visit, and study endpoint with respect to demographic and baseline characteristics, efficacy variables, and safety variables. • Statistical analyses were performed using two-sided tests; 0.05 significance level. • Analysis population defined as all patients in the Intention-to-treat (ITT) population that had at least 70% of 1 circadian cycle of nTST data reported during each screening and post-randomization (N=72). • ITT population included all patients randomized into the study that had τ estimated post-randomization (N=78).
Methods	**Inclusion criteria** • 18-75 years of age • Totally blind patients with no reported light perception (self-reported). • τ ≥ 24.25 hours (95% CI 24.1 – 24.9) based on aMT6s • Sleep-wake complaint as assessed by the Sleep-Wake Questionnaire **Exclusion criteria** • BMI <18 or >33 kg/m^2 • History of other sleep disorders than Non-24 or psychiatric disorders • Night, rotating, or split shift work within one month prior to screening or during the study • Current use of medications that could interfere with the evaluation of circadian rhythms • NSAID use that could not be adequately interrupted for the study's 48-hour urine collections • Drug or alcohol abuse within 12 months of screening • History of smoking >10 cigarettes/day • Creatinine clearance ≤55 mL/min

- Impaired liver function (ALT, AST, or bilirubin > 2 times upper limit of normal)
- Clinically significant abnormalities in other clinical laboratory results, vital signs or physical examination findings at screening

Criteria

	Tasimelteon	Placebo	P-Value
Primary Outcome[1]			
Proportion of patients achieving entrainment based upon aMT6s, n/N (%)[5]	8/40 (20.0%)	1/38 (2.6%)	0.0171
Step-down Primary Outcome[2]			
Clinical response (entrainment + N24CRS ≥3), n/N (%)[6]	9/38 (23.7%)	0/34 (0.0%)	0.028
Secondary Efficacy Outcomes[2]			
Proportion of patients achieving entrainment based upon cortisol, n/N (%)[1]	7/40 (17.5%)	1/38 (2.6%)	0.0313
Mean nTST (minutes)	56.80	17.08	0.0055
Mean dTSD* (minutes)	-46.48	-17.87	0.0050
Mean MoST (minutes)	35.0	14.48	0.0123
Mean CGI-C[¶]	2.6	3.4	0.0093
Post-hoc Analysis[3]			
LQ-nTST minutes	50	22	0.051
UQ-dTSD* minutes	-49	-22	0.012
Exploratory Analysis[4]			
LQ-nTST (minutes)	97.69	15.34	0.0001
UQ-dTSD* (minutes)	-94.58	-20.94	<0.0001

[1]Included all patients randomized that had r post-randomization (N=78); [2] All subjective secondary sleep endpoints were based on patients in the ITT population that had at least 70% of 1 circadian cycle of nTST data reported during each screening and post-randomization (N=72); [3]Conducted on all randomized patients (n=84)-requested by FDA; [4]Responders that had entrained at either Month 1 or Month 7 (Tasimelteon=13; placebo n=34); [5]Entrainment based on the first month; [6]Entrainment based on the first month or seventh month (SET Double-Masked Phase or RESET Run-in-Phase; respectively. [¶] Average the last 2 scheduled assessments (Month 4 and Month 6). * Smaller values indicate improvement.

MT6s= 6-sulfatoxymelatonin; N24CRS = Non-24 Clinical Response Scale; nTST =nighttime total sleep time; dTSD = daytime total sleep time; MoST = midpoint of sleep timing; CGI-C = Clinical Global Impression of Change; LQ-nTST = lower quartile nighttime total sleep time;; UQ-dTSD = upper quartile daytime total sleep time.

Safety Outcome		
	Tasimelteon, n (%) N=42	**Placebo, n (%) N=42**
Any Adverse Event	34 (81.0%)	24 (57.1%)
Any treatment-related Adverse Event*	19 (45.2%)	15 (35.7%)
Any Serious Adverse Event	2 (4.8%)	0 (0%)
Any treatment-related Serious Adverse Event*	0 (0%)	0 (0%)
Discontinuation due to any Adverse Event	3 (7.1%)	2 (4.8%)
Discontinuation due to treatment-related Adverse Events*	3 (7.1%)	1 (2.4%)
Death	0 (0%)	0 (0%)

*Treatment-related indicates all events in which the relationship with study drug was assessed by the investigator as certain, probable, possible, or unassessable

	Adverse Events*

	Tasimelteon (%) N=42	Placebo (%) N=42
Headache	17	7
Increased aminotransferase	10	5
Nightmare/abnormal dreams	10	0
Upper respiratory tract infection	7	0
Urinary tract infection	7	2

*With an incidence >5% and at least twice as high on tasimelteon than on placebo.

Conclusions	• Entrainment of the circadian rhythm to a 24-hour day was achieved in 20% of the patients taking tasimelteon compared to 2.6% with placebo as measured by aMT6s by the first month. Assessing entrainment early per trial design may underestimate the entrainment rate effect. • Entrainment of the circadian rhythm to a 24-hour day was achieved in 17.5% of the patients taking tasimelteon compared to 2.6% with placebo as measured by cortisol by the first month. • Tasimelteon had a clinically meaningful improvement as measured by the assessment of clinical response and the Non-24 Clinical Response Scale • Tasimelteon demonstrated clinically meaningful improvements across a number of sleep/wake parameters controlled by the circadian rhythm including decreasing the amount of daytime sleep, increasing the amount of nighttime sleep, and optimizing the timing of sleep to a desired time compared to placebo. • Tasimelteon showed significant improvements over placebo in global functioning. • Tasimelteon once daily was generally well-tolerated and safe in the studied population. The majority of adverse events were mild or moderate and discontinuation due to adverse events was similar between treatment groups.
Critique	**Strengths** • Randomized, double-blind, placebo controlled, multicenter trial with objective/subjective validated measurements. • Next day residual was measured. No withdrawal as determined by BWSQ was noted. **Limitations** • Study industry sponsored • Small population size (n=84), (although N-24 is rare disease) • Publication of complete study is pending. • Results of study may not be generalized to VA Non-24 population as the study patients had a mean age of 51 and were without co-morbidities that would hinder study participation (see exclusions).

Table 2: Randomized-withdrawal study of the Efficacy and Safety of Tasimelteon to treat Non-24 (RESET) [89,11,16,-17]

Study Goal	Evaluate the ability of tasimelteon to maintain entrainment in totally blind patients with Non-24
	Study Endpoints: • Primary endpoint: proportion of patients who did not maintain entrainment of urinary 6-sulfatoxymelatonin (aMT6s) rhythm to 24 hours, defined as post-baseline tau ≥24.1 or the lower bound of the 95% CI >24.0 • Secondary endpoints: lack of entrainment of urinary cortisol rhythm; measures of total nighttime sleep, daytime nap duration, and midpoint of sleep timing (MoST); replapse.
Methods	**Study Design** • Phase III, multicenter, randomized withdrawal, double-masked, placebo-controlled trial conducted in the United States between September 2011 and December 2012 • Consisted of 2 phases: ○ Pre-randomization phase:

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Open-label tasimelteon run-in phase (~6 weeks): eligible patients were treated with 20 mg/day of tasimelteon
Circadian rhythm estimation phase (~6 weeks): patient's circadian period was estimated using the same methodology as SET

Randomized, double-masked withdrawal phase: patients who achieved entrainment were randomized (1:1) to continue receiving tasimelteon 20mg (n=10) or placebo (n=10) once daily 1 hour prior to target bedtime for an additional 8 weeks

Data Analysis

Not entrained was defined as having a post-baseline τ value ≥24.1 or the lower bound of the 95% CI >24.0
Subjective nighttime sleep and daytime naps were reported twice daily using an electronic interactive voice recording system
Safety was assessed through adverse event reporting, clinical laboratory measures, vital signs, electrocardiograms (EKG), and Tyrer Benzodiazepine Withdrawal Symptoms Questionnaire (BWSQ)
Statistical analyses were performed using two-sided tests with a 0.05 significance level

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<tr><td>Criteria</td><td>
Inclusion Criteria:

Patients who previously participated or screened in the SET study with a circadian rhythm (τ) estimation period >24.1 and a 95% CI that did not include 24, agreeing to commit to a fixed 9-hour sleep opportunity
τ > 24.0 hours

Exclusion Criteria:

Presence of another sleep disorder other than Non-24 was judged to be the primary cause of sleep disturbance
Night, rotating, or split shift work within one month prior to screening or during the study
History of psychiatric disorder that might affect study participation or compliance that was not being effectively treated
Drug or alcohol abuse within 12 months of screening
Non-steroidal anti-inflammatory (NSAID) drug use that could not be adequately interrupted for the study's 48-hour urine collections
History of smoking >10 cigarettes/day
Creatinine clearance ≤55 mL/min
Impaired liver function (ALT, AST, or bilirubin >2 times Upper Limit of Normal
Clinically significant abnormalities in other laboratory results, vital signs, or physical examination findings at screening

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<tr><td>Results</td><td>
Patient Characteristics:

Baseline demographic and clinical characteristics were similar between the treatment groups.
Overall, mean age was 52 ± 12 y ears, 60% were male, 90% were white and not Hispanic or Latino.
Mean baseline τ values measured by aMT6s and cortisol were 24.00 hours and 24.00 hours, respectively.

Efficacy:

Primary Outcome: Proportion of patients who did not maintain entrainment to a 24-hour circadian clock was significantly lower in the group continuing Hetlioz compared to those switched to placebo, as measured by urinary aMTCs and cortisol timing
Secondary outcomes:

<table>
<tr><th></th><th>Hetlioz (n=10)</th><th>Placebo (n=10)</th><th>P-value</th></tr>
<tr><td colspan="4">Primary Outcome</td></tr>
<tr><td>Proportion of patients who did not maintain entrainment based upon aMTCs, (%)</td><td>10%</td><td>80%</td><td>0.0026</td></tr>
<tr><td colspan="4">Secondary Outcomes</td></tr>
<tr><td>Proportion of patients who did not maintain entrainment based upon cortisol, (%)</td><td>20%</td><td>80%</td><td>0.0118</td></tr>
<tr><td>LQ-nTST, LS mean minutes</td><td>-6.6</td><td>-73.8</td><td>0.0233</td></tr>
<tr><td>UQ-dTSD*, LS mean minutes</td><td>-9.6</td><td>49.8</td><td>0.0266</td></tr>
<tr><td>MoST, LS mean minutes</td><td>19.8</td><td>-16.2</td><td>0.0108</td></tr>
<tr><td colspan="4">Abbreviations: aMT6s= urinary 6-sulfoxymelatonin, LQ-nTST=lower quartile of nighttime total sleep time; LS= least squares; MoST= midpoint of sleep timing, UQ-dTSD= upper quartile of daytime total sleep duration. Note: *Smaller values indicate improvement</td></tr>
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<tr><td></td><td>Safety:
• The portion of patients who experienced adverse events was similar between the placebo and treatment groups. No patients experienced a serious adverse event or discontinued the study medication due to adverse events.
<table>
<tr><th></th><th>Hetlioz (n=10)</th><th>Placebo (n=10)</th></tr>
<tr><td colspan="3">Safety Outcome Overview</td></tr>
<tr><td>Any AE, n(%)</td><td>6 (60%)</td><td>4 (40%)</td></tr>
<tr><td>Any treatment- related AE*, n(%)</td><td>4 (40%)</td><td>2 (20%)</td></tr>
<tr><td>Any SAE, n(%)</td><td>0 (0%)</td><td>0 (0%)</td></tr>
<tr><td>Any treatment-related SAE*, n(%)</td><td>0 (0%)</td><td>0 (0%)</td></tr>
<tr><td>Discontinuation due to any AE, n(%)</td><td>0 (0%)</td><td>0 (0%)</td></tr>
<tr><td>Discontinuation due to treatment-related AEs*, n(%)</td><td>0 (0%)</td><td>0 (0%)</td></tr>
<tr><td>Death, n(%)</td><td>0 (0%)</td><td>0 (0%)</td></tr>
</table>
NOTE: *Treatment-related indicates all events in which the relationship with study drug was assessed by the investigator as certain, probable, possible, or unassessable.</td></tr>
<tr><td>Conclusions</td><td>• Tasimelteon 20 mg one hour before bedtime at the same time every day is well tolerated and synchronizes melatonin and cortisol circadian rhythms to a 24-hour clock in totally blind patients with Non-24
• Discontinuation of tasimelteon therapy resulted in a loss of entrainment that corresponded with an approximately 50 minute decrease in nighttime sleep and 60 minute increase in daytime napping
• Chronic therapy with tasimelteon is required to maintain entrainment in totally blind patients with Non-24</td></tr>
<tr><td>Critique</td><td>Strengths
• Study design: randomized, controlled
Limitations
• Small sample size (n=20)
• Relatively short duration (8 weeks after discontinuation of tasimelteon)
• Study industry sponsored
• Publication of complete study is pending.
• Results of study may not be generalized to VA Non-24 population as the study patients had a mean age of 52 and were without co-morbidities that would hinder study participation (see exclusions).</td></tr>
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nTST =nighttime total sleep time; LQ-nTST = lower quartile nighttime total sleep time; dTSD = daytime total sleep time; UQ-dTSD = upper quartile daytime total sleep time; MoST = midpoint of sleep timing; CGI-C = Clinical Global Impression of Change. aMT6 = urinary 6-sulfatoxymelatonin; OLE = open label extension; AE = adverse event; PGI-C – Patient Global Impression of Change; NSAID: non-steroidal anti-inflammatory drug; ALT = alanine transaminase; AST = aspartate transaminase; N24CRS = Non-24 Clinical Response Scale; τ = tau; Non-24: Non-24 Sleep-Wake Disorder